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Birth Outcomes and Natural Gas Development: Methodological Limitations

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We read with interest the article "Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado" by McKenzie et al. (2014). We agree with the authors that it is important to determine whether any adverse health effects may be associated with active natural gas wells, especially for susceptible subpopulations.

On the basis of the prevalence of neural tube and congenital heart defects reported in infants born to mothers that lived within a 10-mile radius of natural gas wells, McKenzie et al. (2014) reported an association between natural gas development and these specific birth defects. They suggested that "potential teratogens"—particularly benzene and polycyclic aromatic hydrocarbons—emitted from the wells, related infrastructures, or drilling processes could be a causal factor related to the health effects. They generally weaved a cautionary tale regarding natural gas development and negative reproductive/developmental consequences. Although we applaud the authors' efforts to investigate potential human health concerns related to oil and gas development, we would like to highlight key weaknesses within the study design that were underemphasized in their article. Specifically, we believe that the chosen exposure metric—inverse distance weighted gas well counts in a 10-mile radius of maternal residence during the child's birth year—is a poor surrogate for an actual (i.e., chemical) exposure that might be causally linked to the outcomes of interest, which severely limits the ability to interpret results. In addition, the exposure metric raises issues regarding the biologic plausibility of benzene as the underlying causal agent for the observed effects.

McKenzie et al. (2014) used the gas well density and the distance of gas wells to maternal residence as a proxy for maternal chemical exposure, including in their count any well listed as "existing" within the Colorado Oil and Gas Information System (COGIS) registry during the entire birth year of the infant. However, the neural plate and heart are known to develop during the first trimester, and it is recognized that this is the critical period of sensitivity for induction of defects due to toxicological insult (Rogers and Kavlock 2008). Thus, it would be more appropriate to limit the maternal exposure metric to a window representative of only the first trimester of pregnancy. Additionally, the first trimester of a pregnancy may fall in a different calendar year than the child's birth. Therefore, the authors may have inaccurately characterized maternal exposures for most subjects and severely misrepresented exposures for some. Although McKenzie et al. briefly noted in their "Discussion" that there was insufficient data to determine well counts tied to trimesters as opposed to birth year, we feel that this limitation is understated considering the potential impact.

We have previously determined that benzene is a highly volatile compound with a short atmospheric residence time and is unlikely to travel long distances from the emission source [Voluntary Children's Chemical Evaluation Program (VCCEP) 2006]; the most relevant benzene exposures occur from nearby sources [Agency for Toxic Substances and Disease Registry (ATSDR) 2007; VCCEP 2006]. Interestingly, when McKenzie et al.'s analysis was restricted to wells within a closer proximity (e.g., 1- and 5-mile radii), results were not significant, leading one to question whether the reported results are truly indicative of a causal relationship or simply an artifact of arbitrarily selected parameters. Further, there are many inactive wells on the COGIS registry, which have different benzene emissions than active wells, a distinction that was not captured by the exposure metric. Moreover, McKenzie et al. implied that a causal link between benzene and congenital heart defects has been established and therefore their exposure proxy is justified—although the cited references do not actually provide such evidence, and current consensus documents do not recognize such an association [ATSDR 2007; International Agency for Research on Cancer (IARC) 2012; Lupo et al. 2010; VCCEP 2006; Wennborg et al. 2005).

McKenzie et al. (2014) acknowledged in their article that there is a "lack of temporal and spatial specificity" in their exposure metric, but they appear to primarily relate this to uncertainties such as potential maternal mobility and relative well activity levels. These are minor concerns compared with the larger issue of whether the chemical of interest and the parameters chosen were meaningful, appropriate, and well categorized. As scientists, we have an obligation to appropriately and effectively communicate to the public not just positive and negative findings but also some sense of the magnitude of risk in order to ensure that we do not create or perpetuate an unnecessary level of alarm. Based on the inherent limitations of this study, including that no true exposure to any chemical was actually measured or modeled and that the proxy exposure metric was weak, the suggested association between specific birth defects and natural gas exploration and production reported by McKenzie et al. (2014) should be viewed cautiously and critically.

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Kristen Fedak, Sherilyn Gross, Megan Jacobsen, and Brooke Tvermoes

Cardno ChemRisk, Boulder, Colorado, USA
E-mail: kristen.fedak@cardno.com

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Birth Outcomes and Natural Gas Development: McKenzie et al. Respond

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The comments of Fedak et al. emphasize points we made in our paper (McKenzie et al. 2014) about the importance of conducting comprehensive and rigorous research on the health

effects of oil and gas development. We dedicated much of our "Discussion" to describing the limitations of our study. However, Fedak et al. have overstated these limitations.

As we stated in our paper (McKenzie et al. 2014), our study was limited by the lack of temporal and spatial specificity in using the density of existing gas wells around the maternal residence in the year of birth as the exposure. That being said, based on studies of maternal residential relocation during pregnancy, it is unlikely that a substantial proportion of subjects relocated during their pregnancy (Lupo et al. 2010; Miller et al. 2010). In addition, lack of temporal and spatial specificity of the exposure assessment would most likely have been similar for mothers with and without adverse outcomes and would have therefore resulted in weakened associations (Ritz and Wilhelm 2008; Ritz et al. 2007). Actual associations may be stronger that what we observed.

Some nondifferential exposure misclassification in the analysis of birth defects likely resulted from using data on wells existing in the birth year rather than in the year in which the first trimester of pregnancy occurred. We do not know the extent and severity of this limitation, but in many cases, it is unlikely that the density of existing wells around the maternal residence would have changed dramatically over a few months.

Our results support Fedak et al.'s statement that the most relevant benzene exposures will occur from nearby sources. Emissions from oil and gas wells are associated with the accumulation of benzene and other volatile organic compounds in the atmospheric surface layer in the general vicinity of oil and gas wells (Helmig et al. 2014). On average, one would expect more benzene emissions, and thus greater potential for benzene exposure, in areas with greater densities of natural gas wells. The results of our main analysis and sensitivity analyses indicate a linear dose response between increasing well density and the prevalence of congenital heart defects: The prevalence of congenital heart defects increases as the potential for benzene exposure increases.

Fedak et al. misinterpret our sensitivity analysis and incorrectly state that the results are insignificant. In the sensitivity analysis, we did not restrict our analysis to 1- and 5-mile radii. Rather, we restricted our exposed group to 2- and 5-mile radii. Restricting the exposure definitions would have provided stronger and more accurate associations if exposure in the narrower radii were more accurate than in the 10-mile radius. Because the restriction to the narrower radii did not markedly change the results, we can infer that the 2-, 5-, and 10-mile radii were similarly accurate.

Fedek et al. also take issue with benzene exposure as a plausible explanation for our findings because they assert that benzene is not a proven teratogen. Lack of direct evidence of causation between benzene and birth defects does not exclude the plausibility of benzene as a teratogen. Some studies have suggested an association between maternal exposure and birth defects (Lupo et al. 2011; Wennborg et al. 2005). Benzene is genotoxic, is known to cross the placenta, and has been associated with fetal demise [Agency for Toxic Substances and Disease Registry (ATSDR) 2007]. Although exposure to benzene is one plausible explanation for the observed associations, we stated in our paper that further research is needed to examine whether benzene is responsible for these associations and that other plausible explanations exist.

Fedek et al.'s comments do not change our findings or conclusions. The results of our study suggest a positive association between greater density and proximity of natural gas wells within a 10-mile radius of maternal residence and greater prevalence of congenital heart defects and possibly neural tube defects, but not oral clefts, preterm birth, or reduced fetal growth. These results and the current trends in production underscore the importance of conducting additional research on the potential health effects of oil and gas development.

The authors declare they have no actual or potential competing financial interests.

Lisa M. McKenzie,[1] Ruixin Guo,[2] Roxana Z. Witter,[1] David A. Savitz,[3] Lee S. Newman,[1] and John L. Adgate[1]

[1]Department of Environmental and Occupational Health, and [2]Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, Colorado, USA; [3]Department of Epidemiology, Brown University, Providence, Rhode Island, USA
E-mail: Lisa.McKenzie@ucdenver.edu

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